Journal of the American College of Cardiology Vol. 52, No. 2, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.03.039

Fracture Risk in Men With Congestive Heart Failure

Risk Reduction With Spironolactone

Laura D. Carbone, MD, MS,*† Jessica D. Cross, MD,*† Syed H. Raza, MD,*† Andrew J. Bush, PHD,‡ Robert J. Sepanski, MS,† Saurabh Dhawan, MD,*† Bilal Q. Khan, MD,*† Malini Gupta, MD,*† Khurram Ahmad, MD,*† Rami N. Khouzam, MD,*† Dwight A. Dishmon, MD,*† Joseph P. Nesheiwat, MD,*† Mohammad A. Hajjar, MD,*† Waqas A. Chishti, MD,*† Wael Nasser, MD,*† Mehwish Khan, MD,*† Catherine R. Womack, MD,*† Tara Cho, BA,*† Ashley R. Haskin, BS,* Karl T. Weber, MD, FACC†

Memphis, Tennessee

Objectives The purpose of this study was to determine whether spironolactone use is associated with fractures in men with congestive heart failure (CHF).

Background In rats with aldosteronism, spironolactone preserves skeletal strength. However, in humans, the relationship of spironolactone to fractures is not known.

Methods The medical records of all male patients with CHF from 1999 to 2005 treated at the Veterans Affairs Medical Center, Memphis, Tennessee, were reviewed (n = 4,735). Odds ratios with 95% confidence intervals of having a fracture associated with spironolactone use were estimated using conditional logistic regression.

Results We identified 167 cases with a single-incident fracture and matched these by age and race to 668 control subjects without fractures. After adjustment for covariates, spironolactone use was inversely associated with total fracture (odds ratio: 0.575; 95% confidence interval: 0.346 to 0.955, p = 0.0324).

Conclusions The use of spironolactone is inversely associated with fractures in men with CHF. (J Am Coll Cardiol 2008;52: 135–8) © 2008 by the American College of Cardiology Foundation

Congestive heart failure (CHF) has its origins rooted in a salt-avid state mediated by neurohormonal activation that includes effector hormones of the renin-angiotensin-aldosterone system (RAAS) (1). Observational studies have suggested an interrelationship between CHF and osteoporosis (2–4). Spironolactone, an aldosterone receptor antagonist, preserves skeletal health in rats with aldosteronism (5). However, the relationship between spironolactone use and fracture risk in humans is controversial (6,7). In this study, we explored the association between spironolactone use and fractures.

Methods

Case and control definitions. After approval from the Veterans Affairs Medical Center (VAMC), Memphis, Tennessee, Institutional Review Board, the medical records (including pharmacy data and radiographs) of all male veterans hospitalized at this VAMC from January 1999 to July 2005 with an International Classification for Diseases–9th edition (ICD-9) code consistent with CHF were reviewed (n = 4,735). A fracture case was defined as any male veteran with a history of CHF and a nontraumatic fracture between 1999 and 2005. Cases with a medical disorder associated with bone metabolism were excluded. Nonfracture control subjects (same exclusions as cases) were men with CHF with no history of a nontraumatic fracture between these dates. We defined nontraumatic fractures as those that occurred with no identifiable trauma or from a fall from less than a standing height (8). A total of 1,655 patients met at least 1 exclusion criteria and were excluded; 189 cases, including 167 with single fractures and 668 control subjects selected at random and matched to cases based on age (±1 year) and race in a 4:1 control/case ratio, were included.

Demographic factors and medications. Age; race; height; weight; cigarette use; prevalent fractures of the hip, vertebrae, and wrist; and exposure to beta-blockers, loop and thiazide diuretics, angiotensin-converting enzyme inhibi-

From the *Department of Veterans Affairs Medical Center, †Department of Medicine, and ‡Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee.

Manuscript received December 5, 2007; revised manuscript received February 15, 2008, accepted March 4, 2008.

JACC Vol. 52, No. 2, 2008
July 8, 2008:135–8

Abbreviations and Acronyms

CHF = congestive heart failure

CI = confidence interval

OR = odds ratio

RAAS = renin-angiotensin-aldosterone system

tors, angiotensin receptor blockers, anticonvulsants, corticosteroids, bisphosphonates, and teriparatide between 1999 and 2005 were recorded. For control subjects, any use of these medications between January 1999 and July 2005 was considered use; for cases, use was between these dates and before the incident fractures. The duration and highest dose of spironolactone used before the index date of the fracture (cases) or between 1999 and 2005 (control subjects) were recorded.

Fracture history. Incident fractures between 1999 and 2005 were included except those related to trauma or to skull, facial, or rib fractures. We included a vertebral fracture if there was a fracture on radiographs between 1999 and 2005 and a radiograph before these dates without a vertebral fracture or a notation that this was an incident fracture. However, for some vertebral fractures, we could not ascertain whether the fracture was incident. This occurred because there was a fracture present on a radiograph between 1999 and 2005 with no prior radiographs and no clinical record of the fracture. Vertebral fractures are important (9); therefore, in our statistical analysis, we ran 2 statistical models for total fractures, 1 including and 1 excluding vertebral fractures.

Statistical analysis. Differences in baseline characteristics and medication use in cases and control subjects (Tables 1 and 2) were determined using *t* tests for continuous variables and chi-square testing for categorical variables. Conditional logistic regression was used to determine odds ratios (ORs) for patients with fractures. Models were adjusted for smoking status, body mass index, prevalent fractures, and other medication exposures that may be associated with bone metabolism. The ORs with 95% confidence intervals (CIs) unadjusted and adjusted for these variables are presented. Duration of exposure (<6 and >6 months) to spironolactone was entered into the model.

Table 1 Selected Characteristics of the Study Population

Characteristic	Cases (n = 167)*	Control Subjects (n = 668)*	p Value
Age (yrs)†	67.74 (10.52)	67.74 (10.39)	0.8186
Race†			
White	74.25%	73.95%	0.9251
Black	20.36%	21.26%	0.8724
Unknown	5.39%	4.79%	0.9113
Body mass index (kg/m^2)	28.37 (7.52)	29.16 (14.29)	0.5313
Smoking status			
Never	16.77%	19.46%	0.5143
Current	38.32%	32.19%	0.1634
Past	39.52%	38.77%	0.8650
Not known	5.39%	9.58%	0.0897

Values given are mean (SD) or percent. *For body mass index: cases n = 163, control subjects n = 631. †Matching variable.

Table 2 Medication Use in Study Population

Characteristic	Cases (n = 167)	Control Subjects (n = 668)	p Value
Cardiac medications			
Beta-blocker	55.42%	65.87%	0.0122
Loop diuretic	77.11%	82.49%	0.1110
Thiazide diuretic	24.39%	32.23%	0.0510
Angiotensin-converting enzyme	68.07%	78.89%	0.0031
Angiotensin receptor blocker	10.24%	9.60%	0.8016
Osteoporosis medications			
Bisphosphonates	6.06%	1.35%	0.0013
Teriparatide	0%	0.15%	1.0000
Other medications			
Corticosteroids	22.42%	14.97%	0.0207
Anticonvulsants	16.87%	13.62%	0.2847

In our analyses, we included a total of 167 cases with single fractures. In a separate analysis of multiple-fracture cases, we included 21 cases age- and race-matched to 84 control subjects and determined crude and adjusted ORs for total fractures.

All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). The p values were 2-sided and were considered statistically significant if $p \leq 0.05$.

Results

Tables 1 and 2 depict clinical characteristics and medication use in the study population. In unadjusted and adjusted models, use of spironolactone was inversely associated with total fractures, OR: 0.480 (95% CI: 0.308 to 0.749), p = 0.0012, and OR: 0.575 (95% CI: 0.346 to 0.955), p = 0.0324, respectively (Table 3). Exclusion of vertebral fractures from the total fracture analysis did not significantly change the results (data not shown). Analysis of the multiple fracture data also revealed a significant crude and adjusted inverse association of spironolactone use with total fractures, OR: 0.120 (95% CI: 0.015 to 0.938), p = 0.0433, and OR: 0.092 (95% CI: 0.009 to 0.964), p = 0.0465. There was no significant association of spironolactone use with hip (or site of hip), wrist, or vertebral fractures (Table 3). However, in both unadjusted models, OR: 0.381 (95% CI: 0.162 to 0.897), p = 0.0272, and adjusted models, OR: 0.236 (95% CI: 0.077 to 0.726), p = 0.0118, use of spironolactone was inversely associated with the category of other fractures (Table 3). In unadjusted models, there was a significant inverse association of spironolactone use with nonvertebral fractures, OR: 0.508 (95% CI: 0.289 to 0.894), p = 0.0189, with a trend after adjustment for covariates, OR: 0.550 (95% CI: 0.286 to 1.058), p = 0.0733.

There were too few users of doses of spironolactone >25 mg/day to determine the association between dose of spironolactone and fractures. In adjusted models, long-term (>6 months) exposure to spironolactone was inversely

Table 3 Relationship of Use of Spironolactone to Fractures (vs. Nonuse)

Fracture Site	Cases	Control Subjects	Crude Odds Ratio (95% CI)	p Value	Adjusted Odds Ratio (95% CI)*	p Value
Total	167	668	0.480 (0.308–0.749)	0.0012	0.575 (0.346–0.955)	0.0324
Hip	36	144	0.547 (0.218–1.375)	0.1998	0.848 (0.255–2.825)	0.7889
Wrist	10	40	1.126 (0.249–5.105)	0.8774	—	—
Vertebral	69	276	0.438 (0.213–0.902)	0.0251	0.581 (0.252–1.343)	0.2041
Other	52	208	0.381 (0.162–0.897)	0.0272	0.236 (0.077–0.726)	0.0118

*Adjusted for smoking, body mass index, prevalent fracture, and medication exposures.
CI = confidence interval.

associated with total fractures, OR: 0.555 (95% CI: 0.313 to 0.981), p = 0.0428 (Table 4).

Discussion

Patients with cardiovascular disease, including those with CHF (4), are a population at substantial risk for osteoporotic-related fractures (10–12). Spironolactone is increasingly being used to treat hypertension and CHF (13), particularly diastolic dysfunction (14). In this large, veterans-based study of men with CHF, long-term use of spironolactone (>6 months) was inversely associated with total incident fractures.

On a population basis in the U.S., fractures other than the hip/pelvis, vertebrae, and wrist account for approximately one-third of all incident fractures and 14% of all cost expenditures (15). In our study, spironolactone use was inversely associated with the category of other fractures, but not with hip fractures. Particularly in men, hip fractures are associated with substantial mortality (16). This lack of association of spironolactone with hip fractures may be because hip fracture prevention from drugs used to treat osteoporosis requires long-term use (17,18). Alternatively, most hip fractures result from a fall (19), and spironolactone may not be associated with fall risk. Even at the low doses of spironolactone used in our study (mean dose 25 mg/day), there was an inverse association with fractures. This has important therapeutic implications because in clinical practice, low rather than high doses of spironolactone are more commonly prescribed (20,21).

There are several potential mechanisms that may explain our findings. Spironolactone antagonizes aldosterone receptor binding, and aldosteronism in rats is associated with bone loss and a reduction in bone strength to flexor stress that can be rescued by this drug (5,22). In addition, spironolactone may decrease calcium and magnesium excretion and increase potassium (5,13,14); these may have important skeletal implications (23,24).

Study limitations. There are several limitations to our study. Our results are retrospective, and are confined to men, to a single VAMC, and to one aldosterone antagonist. The number of hip, vertebral, and wrist fractures was small, and the study may have been underpowered to detect an association of spironolactone with site-specific fractures. Testosterone levels were not uniformly available. This may be particularly important because spironolactone has antiandrogenic properties (25). We did not have uniform data on renal or vitamin D insufficiency or other comorbidities, all of which are associated with fracture risk (26–28). Similarly, we did not have information on calcium intake or alcohol use, which are important determinants of fracture risk (29,30). We did not include use of warfarin or statins in our analyses; these medications have been associated with fracture risk in some (31,32), but not all (33,34), studies. Finally, some veterans may have received care for fractures outside of the Veterans Affairs medical system. In summary, because of these limitations, it is entirely possible that the inverse association of spironolactone use with fractures in this population is not from the drug per se, but simply reflects that a more robust, less frail, population was prescribed this drug.

Our study has several unique strengths. The individual chart review by a trained physician abstractor allowed us to capture many more fractures, including those treated outside of our VAMC, than we would have identified by computer-generated identification using ICD-9 codes alone. Most importantly, this is the first, to our knowledge, determination of the association between spironolactone and fractures and is an example of research bridging "the bench to the bedside."

Table 4 Relationship of Duration of Use of Spironolactone to Total Fractures (vs. Nonuse)

Duration of Spironolactone Use	Crude Odds Ratio (95% CI)	p Value	Adjusted Odds Ratio (95% CI)*	p Value
≤6 months (n = 71)	0.406 (0.189–0.876)	0.0216	0.633 (0.276–1.447)	0.2781
>6 months (n = 156)	0.513 (0.311–0.847)	0.0090	0.555 (0.313–0.981)	0.0428

*Adjusted for smoking, body mass index, prevalent fracture, and medication exposures.
CI = confidence interval.

Conclusions

In conclusion, there is an inverse association between spironolactone use and total fractures in men with CHF. Further studies, including randomized clinical trials of spironolactone use with bone mineral density and fracture end points in men and women with CHF, should be considered.

Reprint requests and correspondence: Dr. Karl T. Weber, University of Tennessee Health Science Center, Division of Cardiovascular Diseases, 920 Madison Avenue, Suite 300, Memphis, Tennessee 38163. E-mail: KTWeber@utmem.edu.

REFERENCES

1. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689–97.
2. Farhat GN, Strotmeyer ES, Newman AB, et al. Volumetric and areal bone mineral density measures are associated with cardiovascular disease in older men and women: the Health, Aging, and Body Composition Study. Calcif Tissue Int 2006;79:102–11.
3. Nishio K, Mukae S, Aoki S, et al. Congestive heart failure is associated with the rate of bone loss. J Intern Med 2003;253:439–46.
4. Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med 1997;103:197–207.
5. Chhokar VS, Sun Y, Bhattacharya SK, et al. Hyperparathyroidism and the calcium paradox of aldosteronism. Circulation 2005;111:871–8.
6. Moghetti P, Castello R, Zamberlan N, et al. Spironolactone, but not flutamide, administration prevents bone loss in hyperandrogenic women treated with gonadotropin-releasing hormone agonist. J Clin Endocrinol Metab 1999;84:1250–4.
7. Prezelj J, Kocijancic A. Antiandrogen treatment with spironolactone and linestrenol decreases bone mineral density in eumenorrhoeic women with androgen excess. Horm Metab Res 1994;26:46–8.
8. Brown JP, Josse RG, Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167 Suppl: S1–34.
9. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR, the Study of Osteoporotic Fractures Research Group. Which fractures are associated with low appendicular bone mass in elderly women? Ann Intern Med 1991;115:837–42.
10. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA, Study of Osteoporotic Fractures Research Group. High blood pressure and bone-mineral loss in elderly white women: a prospective study. Lancet 1999;354:971–5.
11. Nawroth P, Pirzer R, Fohr B, et al. Osteoporosis and cardiovascular disease—two sides of the same coin [in German]? Med Klin (Munich) 2003;98:437–46.
12. Tanko LB, Bagger YZ, Christiansen C. Low bone mineral density in the hip as a marker of advanced atherosclerosis in elderly women. Calcif Tissue Int 2003;73:15–20.
13. Mantero F, Lucarelli G. Aldosterone antagonists in hypertension and heart failure. Ann Endocrinol (Paris) 2000;61:52–60.
14. Roongsritong C, Sutthiwan P, Bradley J, Simoni J, Power S, Meyerrose GE. Spironolactone improves diastolic function in the elderly. Clin Cardiol 2005;28:484–7.
15. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J Bone Miner Res 2007; 22:465–75.
16. Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner J. Gender differences in mortality after hip fracture: the role of infection. J Bone Miner Res 2003;18:2231–7.
17. Liberman UA, Hochberg MC, Geusens P, et al. Hip and non-spine fracture risk reductions differ among antiresorptive agents: evidence from randomised controlled trials. Int J Clin Pract 2006;60:1394–400.
18. Silverman SL, Watts NB, Delmas PD, Lange JL, Lindsay R. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the Risedronate and Alendronate (REAL) Cohort Study. Osteoporos Int 2007;18:25–34.
19. Silva MJ. Biomechanics of osteoporotic fractures. Injury 2007;38 Suppl 3:S69–76.
20. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.
21. Calhoun DA. Low-dose aldosterone blockade as a new treatment paradigm for controlling resistant hypertension. J Clin Hypertens (Greenwich) 2007;9:19–24.
22. Chhokar VS, Sun Y, Bhattacharya SK, et al. Loss of bone minerals and strength in rats with aldosteronism. Am J Physiol Heart Circ Physiol 2004;287:H2023–6.
23. Macdonald HM, New SA, Fraser WD, Campbell MK, Reid DM. Low dietary potassium intakes and high dietary estimates of net endogenous acid production are associated with low bone mineral density in premenopausal women and increased markers of bone resorption in postmenopausal women. Am J Clin Nutr 2005;81:923–33.
24. Kitchin B, Morgan SL. Not just calcium and vitamin D: other nutritional considerations in osteoporosis. Curr Rheumatol Rep 2007; 9:85–92.
25. Carmina E. Anti-androgens for the treatment of hirsutism. Expert Opin Investig Drugs 2002;11:357–63.
26. Fried LF, Shlipak MG, Stehman-Breen C, et al. Kidney function predicts the rate of bone loss in older individuals: the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci 2006;61:743–8.
27. Meier C, Woitge HW, Witte K, Lemmer B, Seibel MJ. Supplementation with oral vitamin D_3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. J Bone Miner Res 2004;19:1221–30.
28. Colon-Emeric CS, Pieper CF, Artz MB. Can historical and functional risk factors be used to predict fractures in community-dwelling older adults? Development and validation of a clinical tool. Osteoporos Int 2002;13:955–61.
29. Meier C, Nguyen TV, Center JR, Seibel MJ, Eisman JA. Bone resorption and osteoporotic fractures in elderly men: the Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res 2005;20:579–87.
30. Mukamal KJ, Robbins JA, Cauley JA, Kern LM, Siscovick DS. Alcohol consumption, bone density, and hip fracture among older adults: the Cardiovascular Health Study. Osteoporos Int 2007;18:593–602.
31. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med 2006;166:241–6.
32. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Effects of statins on bone mineral density: a meta-analysis of clinical studies. Bone 2007;40:1581–7.
33. Jamal SA, Browner WS, Bauer DC, Cummings SR, Study of Osteoporotic Fractures Research Group. Warfarin use and risk for osteoporosis in elderly women. Ann Intern Med 1998;128:829–32.
34. LaCroix AZ, Cauley JA, Pettinger M, et al. Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. Ann Intern Med 2003;139:97–104.

Key Words: congestive heart failure ■ spironolactone ■ men ■ medical records.